UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,543	07/10/2003	Harvey Ellis Cline	124387	4286

6147 7590 05/15/2007
GENERAL ELECTRIC COMPANY
GLOBAL RESEARCH
PATENT DOCKET RM. BLDG. K1-4A59
NISKAYUNA, NY 12309

EXAMINER	
RAMIREZ, JOHN FERNANDO	

ART UNIT	PAPER NUMBER
3737	

MAIL DATE	DELIVERY MODE
05/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

PTOL-90A (Rev. 04/07)

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

MAILED

MAY 15 2007

GROUP 3700

Application Number: 10/617,543
Filing Date: July 10, 2003
Appellant(s): CLINE ET AL.

Jean K. Testa
General Electric Company
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 5, 2006 appealing from the Office action mailed on February 24, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5322682	Bartzokis et al.	6-1994
5603322	Jesmanowicz et al.	2-1997
6294972	Jesmanowicz et al.	9-2001

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **1-3, 6-12, and 13** are rejected under 35 U.S.C. 103(a) as being unpatentable over Bartzokis et al (U.S. Pat. 5,322,682) in view of Jesmanowicz et al. (U.S Pat. 5,603,322).

5

The invention and its various embodiments may now be understood by turning to the following detailed description.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention provides a specific measure of iron stores in vivo using magnetic resonance imaging. The T_2 of tissue in both lower-to-mid field strength magnetic resonance imaging instruments and a higher field strength instrument is evaluated. T_2 obtained by the higher field strength instrument is subtracted from T_2 obtained by the lower field strength instrument or vica versa. This difference, T, obtained in vivo is then correlated with a quantitative measure of the iron stores in vivo in the scanned tissue. A two-dimensional or multi-dimensional map of the scanned tissue is then constructed on the basis of T to visually identify different tissue types as being normal or abnormal, either through a visual determination based on gray scales or a numeric comparison based on quantitative measure. The introduction of artificial or nonbiological substances as opposed to natural ferritin, is permitted for further diagnostic use.

Regarding **Claim 1,** the **Bartzokis** reference discloses "a specific measure of iron stores in vivo using MRI. The T_2 tissue in both lower to mid filed strength MRI instruments and a higher field strength instrument is evaluated" (see above) (column 5, lines 6-13). The Bartzokis reference is lacking a tool used to acquire images by a pulse sequence, where as the Jesmanowicz'322 reference discloses "a pulse sequence which is performed by an NMR system which acquires 128 images of the brain" (See Abstract). Also, the **Jesmanowicz'322** reference mentions that the region of interest is scanned by a sequence of NMR measurement cycles that vary accordingly depending on the volume of iron deposits. It would be obvious to one having an ordinary skill in the art to combine an image acquiring tool by pulse sequence, with the Bartzokis reference to provide a better method for iron detection in a selected region.

9

the axial images at the midpoint of the phantom tubes. All other further protocols and procedures were carried out exactly for both the 0.5 Tesla and 1.5 Tesla studies.

In both the in vivo and in vitro MRI examples, identical Carr Purcell Melboom Gill two spin-echo sequences (TR=2500, TE=20,90) with two signals averaged, at 192 gradient steps, 3 millimeter slice thickness, and 25 centimeter field of view were used. It is expressly contemplated that other sequences could be used, such as gradient echo sequences that quantify T_2^*. Any sequence that included a T_2 influence could be used, since the differencing step enhances the field dependant effects. All further calculations and data extraction procedures again were carried out exactly for both the 0.5 and 1.5 Tesla studies. The T_2 values were calculated using system software and the T_2 data was extracted. T_2 was calculated for each voxel by an automated algorithm from the two (TE=20,90) signal intensities of the two spin-echo sequences to produce gray scale encoded T_2 maps of the brain and the phantoms as demonstrated in the photograph of FIG. 1.

Regarding **claim 2, and 12,** the Jesmanowicz'322 reference lacks dual gradient pulse sequence where as the Bartzokis reference Figure 1 illustrates signal intensities of the two spin-echo sequences to produce gray scale encoded T_2 maps of the brain. It would have been obvious to one having ordinary skill in the art to combine the dual echo sequencing with a pulse sequence image acquiring system that would provide a better analysis. (see above, column 9, lines 4-21).

Regarding **claims 3, and 13,** the Jesmanowicz'322 reference lacks a step that generates a 3 D field map of the brain whereas, the Bartzokis reference discloses, "a two dimensional or multidimensional map of the scanned tissue is constructed on the basis of T to visually identify different tissue types as being normal or abnormal" (column 5, lines16-18). It would have been obvious to one having ordinary skill in the art to combine the pulse sequencing method of the Jesmanowicz'322 reference (image acquisition by pulse sequence) with the Bartzokis reference to have a multidimensional map of the scanned tissue, which would eventually help in a better diagnosis.

1

METHOD FOR QUANTITATIVELY MEASURING AND MAPPING STORED IRON IN TISSUE USING MRI

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to the field of the use of magnetic resonance in medicine to measure iron stores in tissue, and in particular to quantitatively and specifically measure in vivo ferritin and closely related substances in tissue.

2. Description of the Prior Art

During the past decade, a number of studies have implicated iron as a central culprit in various diseases including some cancers. A genetic disease, hemochromatosis, which causes excessive accumulations of iron in tissue and which can be fatal, is estimated to occur or to be at risk in an estimated 1.4 million Americans. The accumulation of iron stores in tissue has also been implicated in various studies in liver damage, arthritis, diabetes, impotence, heart failure and various neurological disorders such as Alzheimer's and Parkinson's disease. Iron stores is understood to mean ferritin or ferritin like proteins, which is the biological form for storage of iron.

Regarding **claims 6, and 11,** the Jesmanowicz'322 reference lacks an indicative method that would suggest the presence of diseases like Alzheimer's, Parkinson's, Huntingtion and other neurodegenerative diseases. Where as the Bartzokis reference discloses "the accumulation of iron stores in tissue has been implicated in various neurological disorders such as Alzheimer's and Parkinsons disease" (see above) (column 1,lines 20-24). It would have been obvious to one having an ordinary skill in the art at the time of the invention to combine iron detection methods as disclosed by Bartzokis with the pulse image sequencing of Jesmanowicz'322 to provide an accurate iron detection that would help in the diagnosis of any neurodegenerative diseases.

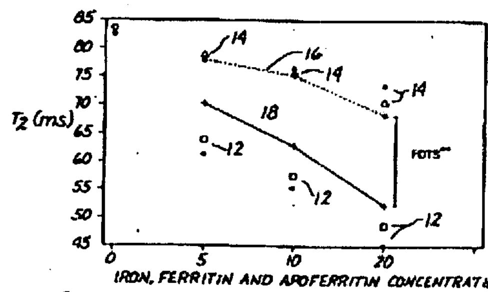


Fig. 2

IRON, FERRITIN AND APOFERRITIN CONCENTRATIONS (SEE TEXT)

FIELD STRENGTH:	1.5T	.5T
FERRITIN		
IRON	•	▫
APOFERRITIN	•	•
AGAROSE GEL	•	•

* MEAN OF TWO INDEPENDENT MEASURES ** FIELD DEPENDENT T_2 SHORTENING (FOTS) DEFINED AS THE DIFFERENCE IN THE MEANS OF CALCULATED T_2 VALUES OBTAINED USING THE TWO FIELD STRENGTH INSTRUMENTS.

Regarding **Claims 7, and 10,** the Bartzokis reference illustrates a graph showing the period 12 as measured in vitro against ferritin and apoferritin concentrations as measured in 1.5 and .5 Tesla fields (see Figure 2 above). This clearly shows that tests were conducted at a strength of 1 .5 Tesla and it is an obvious to use a higher magnetic field strength in order to detect iron deposits in a selected tissue.

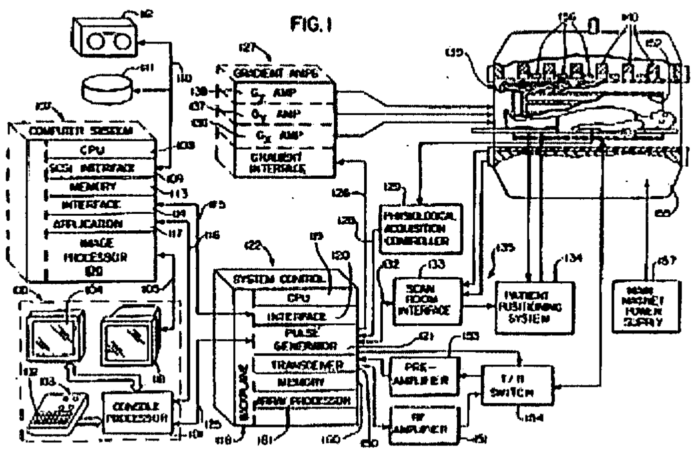
In the illustrated embodiment, the step of measuring T_2 at the first field strength is performed on a first magnetic resonance imaging instrument and the step of measuring T_2 at the second field strength is measured on a second magnetic resonance imaging instrument. The method further comprises the step of immobilizing the subject in at least one standardized position. The step of immobilizing comprises the step of positioning the subject within the magnetic resonance imaging instruments to assume a predetermined position of each of the instruments with respect to at least one standard anatomical reference point with respect to the subject.

The steps of measuring are repeated within a selected tissue region within the subject in order obtain minimum statistical deviation of measurements within the tissue region. Another way to measure is to measure the entire region and take the T_2differences on a point-by-point basis followed by calculation of a statistical measure for the entire region. Still another way to measure

Regarding **claim 8,** the Jesmanowicz'322 reference lacks the repeating of the image acquiring steps in the tissue, whereas the Bartzokis reference discloses "the steps of measuring are repeated within a selected tissue region within the subject in order to obtain minimum statistical deviation of measurements within the tissue region" (see above) (column 3, lines 62-65). It would have been obvious to one having ordinary

skill in the art to repeat the steps of measurement within the selected region of interest to provide a better understanding of the disease and to monitor the progression.

FIG. 1



Regarding **claim 9,** the Jesmanowicz'322 reference illustrates an MRI device in Figure 1 (above), the system shows the different components such as the CPU, pulse generator, controls, image processor etc. Where as the Bartzokis reference discloses a method for measuring iron stores in vivo using MRI, where it is processed through a 2D or a multidimensional map of the scanned tissue. It would be obvious to one having ordinary skill in the art to combine the system used in the Jesmanowicz'322 reference with the methods of measuring iron as said in the Bartzokis reference to better monitor the selected region of interest of the brain.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **4, 5, 14, and 15** are rejected under 35 U.S.C. 103(a) as being unpatentable over Bartzokis et al (U.S. Pat. 5,322,682) in view of Jesmanowicz et al. (U.S Pat. 5,603,322) and in further view of Jesmanowicz et al. (U.S. Pat. 6,294,972).

8

the region of interest it is substantially equal in magnitude and opposite in sign to that of the field whose homogeneity is to be improved. Thus the summation of the two fields result in a field whose magnitude excursions are substantially smaller, i.e., the magnetic field is more homogeneous. The objective is to calculate a suitable quantity of ferromagnetic material to be appropriately distributed around the region whose magnetic field homogeneity is to be improved. As will be described in more detail below, in the preferred embodiment of the invention, the magnetic field indicated by the field map is decomposed into components. These components are then nulled by calculating an array of ferromagnetic elements that produce equivalent field components that are substantially equal in magnitude and opposite in sign to the decomposed field map components. This method gives control over the whole region of interest and allows the resultant field to be calculated not just at the points that were mapped but at any point in the region of interest.

Magnetic fields may be represented in terms of an infinite series of orthogonal functions known as spherical harmonics. Each harmonic consists of the product of a field term and a source term. The field term determines the spatial variation of that harmonic and the source term defined its strength. The field term consists of the product of an Associated

Regarding **claims 4, and 14,** the Bartzokis and the Jesmanowicz'322 reference are lacking a field map of the brain using spherical harmonics where as the **Jesmanowicz'972** discloses "a local coil for acquiring NMR images of a selected part of a subject such as the human brain" (column 1, lines 10-12). Also, he states " Magnetic fields may be represented in terms of an infinite series of orthogonal functions known as spherical harmonics. Each harmonic consists of the product of a field term and a source term. The field term determines the spatial variations of that harmonic and the source term defined its strength" (see above) (column 8, lines 20-25). Additionally, the reference discloses " In the preferred embodiment the field map is decomposed into

49 spherical harmonics" (column 8, lines 56-59). It would be obvious to one having an ordinary skill in the art to combine the method of spherical harmonics with the Bartzokis reference in order to enhance the image quality of the selected region of the tissue.

> ming process to follow.
>
> As indicated at process block 146 a linear programming method is employed to calculate the ideal thickness of ferroshim inserts 72 at each grid location. The preferred design method involves the use of linear programming techniques such as that described by Dorri et al in U.S. Pat. No. 5,045,794. However, the constraints, instead of being applied to magnetic fields measured at the points as described therein, are applied to the magnitudes of the various harmonic source terms that must be nulled so as to reduce the total field variations throughout the region of interest and also to other, generally higher order terms, that must be controlled to avoid introducing field inhomogeneity components that were not present in the original field map.
>
> The linear programming problem should be set up as follows.

Regarding **claims 5 and 15,** the Bartzokis and the Jesmanowicz'322 reference are lacking variations in the magnetic field where as the Jesmanowicz'972 discloses "Each harmonic consists of the product of a filed term and a source term. The filed term determines the spatial variation of that harmonic and the source term defined its strength" (Column 8, lines 22-24). Additionally, the reference states various harmonic source terms must be nulled to reduce the total field variations throughout the region of interest (see above)(Column 10, lines 45-55). It would be obvious to one having an ordinary skill in the art to subtract the spherical harmonic series to measure the variations of the magnetic field in the selected region.

(10) Response to Argument

In relation to the arguments pertaining to **claims 1 and 9**, wherein applicant alleges that the cited references do not disclose a "**magnetic field map**", the examiner

of record notes that both, Bartzokis et al. and Jesmanowicz'322 disclose the use of a " magnetic field map".

In column 5, lines 2-24, Bartzokis et al. discloses a methodology wherein " The T_2 of tissue in both lower-to-mid field strength magnetic resonance imaging instruments and a higher field strength instrument is evaluated to create a two-dimensional map. Importantly, the resulting map is a "magnetic field map" utilized to visually identify different tissue types.

Moreover, the Jesmanowicz'322 patent discloses in column 15, lines 30-49, the step of creating a NMR two-dimensional flat map of the brain. Additionaly, in column 5, lines 1-67, and column 6, lines 1-8, the specification discloses the use of a "magnetic field map".

Applicant's definition of the term "magnetic field map" is referring to measurements acquired during MRI to estimate the constant and linear components of the magnetic field inhomogeneity (see paragraph 0021). Accordingly, the Bartzokis et al. patent provides a method to measure iron stores in vivo using magnetic resonance imaging. The T_2 of tissue in both lower-to-mid field strength and a higher field strength magnetic resonance imaging instrument is evaluated (see abstract). The results provide evidence that T_2 values which are obtained with high field clinical instruments are dependent on the ferritin content of the tissue and that the field dependent shortening is useful as a specific quantitative measure of the ferritin content of the tissue (col. 10, lines 17-23). There are multiple possible explanations for the field dependent T_2 shortening produced by ferritin. One explanation is that the field inhomogeneity created

by the heterogeneous distribution of paramagnetic ferric iron atoms in the ferritin core shorten the observed T_2 to a greater extent in higher than in lower field strength instruments (col. 10, lines 45-51). T_2 obtained by the higher field strength instrument is subtracted from T_2 obtained by the lower field strength instrument or vice versa. This difference, T, obtained in vivo is then correlated with a quantitative measure of the iron stores in vivo in the scanned tissue. A two-dimensional or multidimensional map of the scanned tissue is then constructed on the basis of T to visually identify different tissue types as being normal or abnormal, either through a visual determination based on gray scales or a numeric comparison based on quantitative measure (col. 5, lines 11-21).

A highly significant correlation is found between the brain region and the field strength. The reduction of T_2 by ferritin at the high field strength refers to the magnetic field inhomogeneity created by the distribution of ferric iron concentrations of various brain structures.

In relation to the arguments pertaining that the Bartzokis et al. reference does not teach or suggest "**acquiring MR images at a substantially high magnetic field strength by a pulse sequence adapted to create a magnetic field map of the brain**".

In column 7, lines 33-42, Bartzokis et al. discloses acquiring MRI images with other field strengths could be used which would optimize the T measure.

In column 9, lines 4-39, Bartzokis et al. teaches a method to acquire MRI images at the substantially high magnetic field strength by a pulse sequence to create a magnetic field map of the brain.

In response to appellant's arguments arguing that there is no reasonable basis for modifying or combining the Bartzokis et al. system and method with the Jesmanowicz'322 with respect to the rejection of **claims 1-3, 6-12 and 13**.

The examiner notes for the record that "While there must be some teaching, reason, suggestion, or motivation that the references be combined to arrive at the claimed invention, there is no requirement that the references explicitly suggest the combination. **In re Nilssen**, 851 Fl.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1989). The suggestion or motivation to combine the references or teachings can derive solely from the existence of a teaching, which one of ordinary skill in the art would be presumed to know, and the use of that teaching to solve the same or similar problem which it addresses. **In re Wood**, 599 F.2d 1032, 1037, 202 USPQ 171, 174 (CCPA 1979)".

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

John F. Ramirez
Patent Examiner
Art Unit 3737

December 4, 2006

Conferees:

Ms. Janet Baxter
TQAS ~~SPE~~ Technology Center 3700

Mr. Brian Casler
SPE Art Unit 3737

BRIAN L. CASLER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 3700

General Electric Company
Building K1 Room 4A60
Schenectady, New York 12301